SUPPLEMENTARY MATERIAL

Author contributions

HL did all chromatin profiling experiments, MR did the capture-HiC experiments with data-analysis and figure preparation, NdL and JYH-K delivered the Dutch deletion frequency data, AJ did the human fetal brain cell *LRFN5* expression test, BIH, SB, DdB, SM and MS gave valuable input during the experimental and scientific process and participated in analyzing the data. GH counselled the patients and families, designed the research project, wrote research applications, plotted and analysed chromatin and allele frequency data, made most of the figures and all tables, and wrote the manuscript. All authors have reviewed and approved the final version.

Supplementary Table 1

Targeted MLPA-based DNA methylation results in the genomic area underlying the mega-TAD-peak in a small group of selected individuals. Please note that the normal male with the A-haplotype was hemi-methylated in a position fully methylated in other individuals.

Individual	**Haplo-type**	**TAD-peak lncRNA CpG** 42529925-6*	**TAD-peak lncRNA CpG** 42529958-9*	**TAD-peak conserved CpG** 42498027-8*	**TAD-peak conserved CpG** 42498046-7*
ASD male	A	~100%	~100%	~10%	~10%
ASD male	A	~100%	~100%	~5%	~5%
Normal male	A	~100%	~50%**	~5%	~5%
Normal female	A	~100%	tech. failure	~20%	~20%
ASD male	-	~100%	~100%	~10%	~10%
ASD male	-	~100%	~100%	~10%	~10%
Normal male	-	~100%	~100%	~10%	~10%
Normal female	-	~100%	~100%	~10%	~10%
Normal female	D	~100%	~100%	~50%	~50%
Normal female	C	~100%	~100%	~20%	~20%

*CpG positions corresponding to the mega-TAD peak on chromosome 14 are according to GRCh37. Haplotypes are according to Extended Data Table 1, i.e. all from individuals with a small locus deletion. ** Sanger sequencing verified that this finding was not due to a SNP, i.e. a C to T transition.

Figure S1

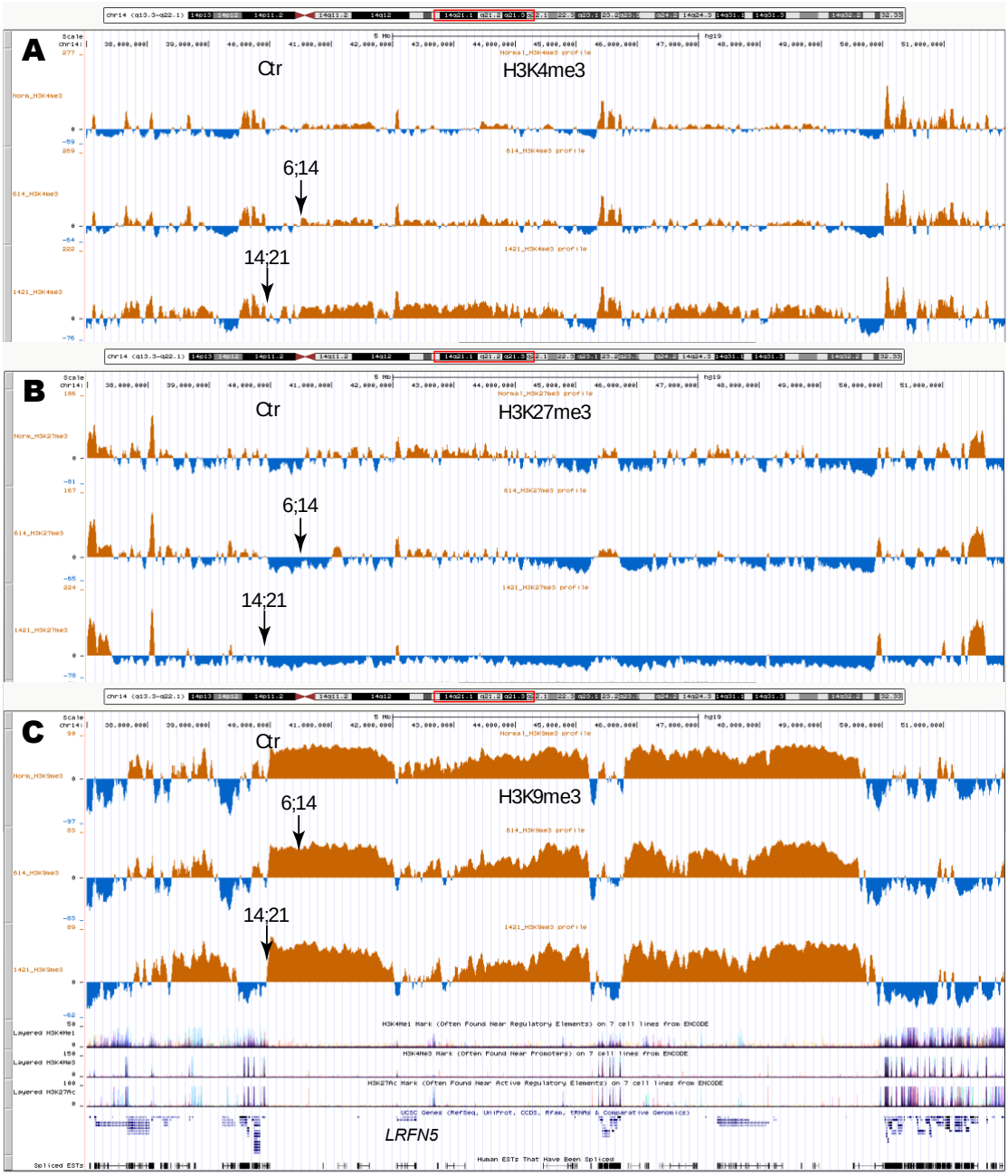

Figure S1

14q21 chIP-on-chip chromatin profiles from a male control (Ctr), a male with Coffin-Siris syndrome and a *de novo* 6;14 translocation disrupting *ARID1B* (6;14), and a female with a *de novo* 14;21 translocation and severe ID/ASD (14;21). The arrows indicate approximate (FISH verified) translocation breakpoints. A: H3K4me3

profiles, B: H3K27me3 profiles, C: H3K9me3 profiles. Only the 14;21-chromatin pattern is markedly different from the Ctr and 6;14 cases: The H3K4me3 and H3K27me3 profiles for the *LRFN5* locus on derivative chromosome 21 show a more "open" chromatin pattern, and the H3K9me3 profiles upstream of the *FBXO33* gene on derivative chromosome 14 (upstream of 14;21 arrow marking the translocation breakpoint) show a more "closed" chromatin pattern. Possibly this is because the translocation fused the *LRFN5* locus to an acrocentric p-arm.

Figure S2

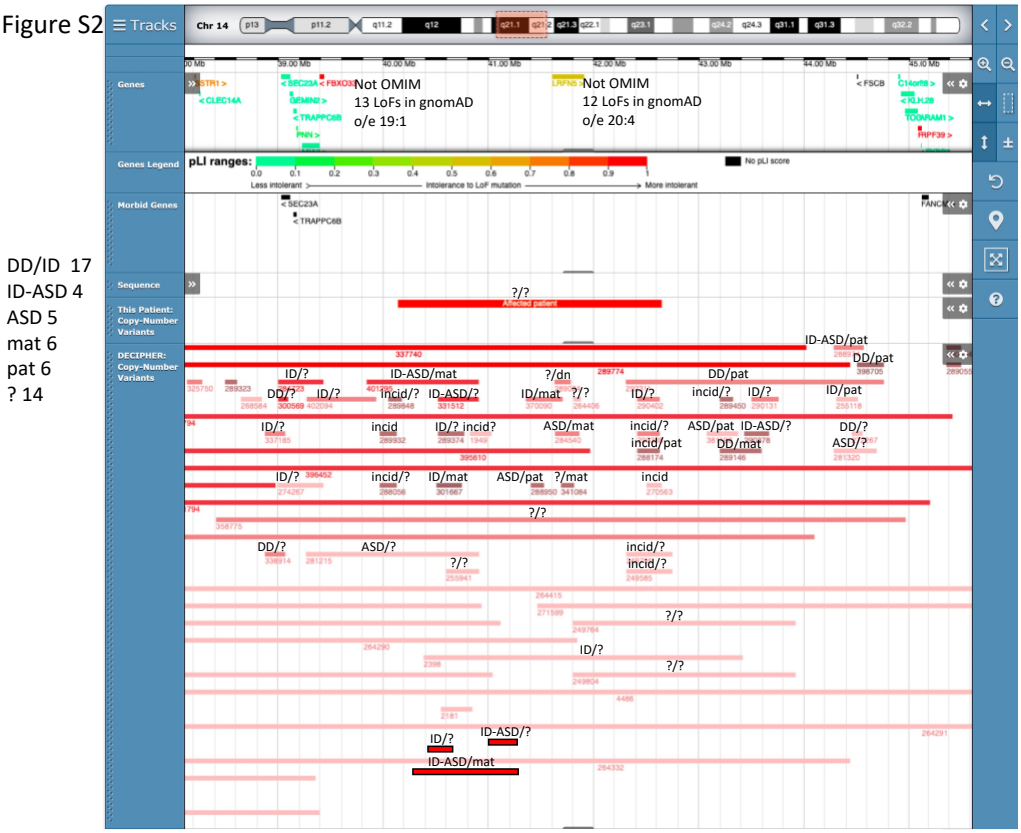

Figure S2

Overview of *LRFN5* locus deletions registered in DECIPHER. The registered phenotype is shown above the deletion: ID = intellectual disability, DD = developmental delay, ASD = autism spectrum disorder, incid? = likely incidental finding (no phenotype recorded), mat = maternally inherited, pat = paternally inherited. On the bottom, three deletions found in own patient records are shown (red lines framed in black). The vertical green shades indicate *LRFN5* locus regions were CNVs appear to be of no clinical consequence. The vertical red shades indicate *LRFN5* locus regions where CNVs could increase susceptibility for DD/ASD.

Figure S3

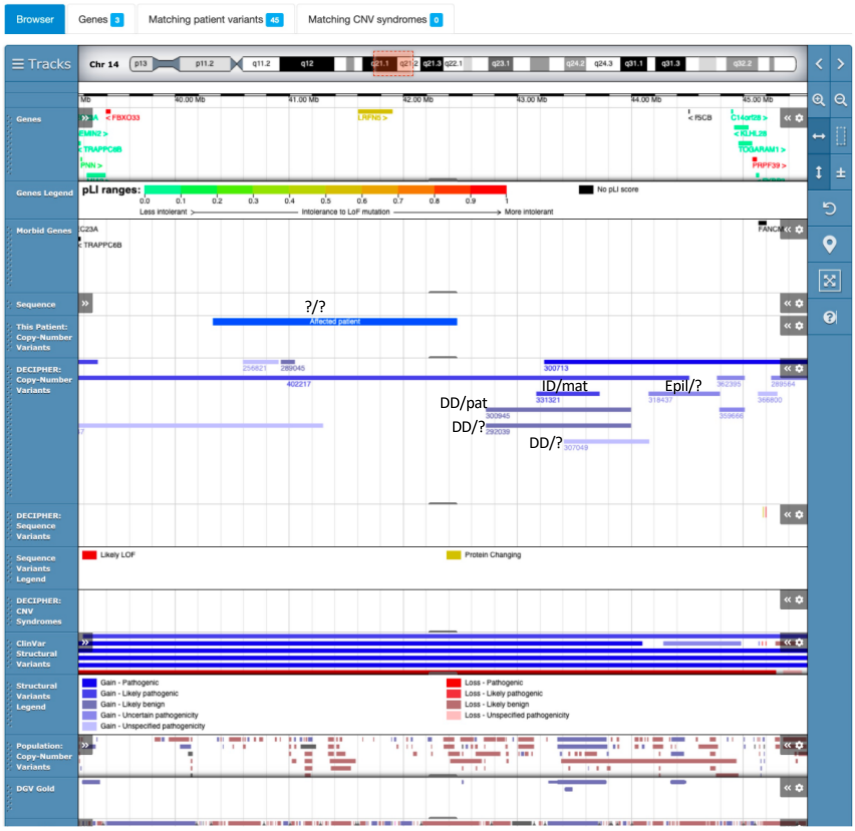

Figure S3

Overview of *LRFN5* locus duplications registered in DECIPHER. The registered phenotype is shown above the deletion: ID = intellectual disability, DD = developmental delay, epil = seizures, mat = maternally inherited, pat = paternally inherited. Note that duplications are rarer than deletions in this region, which is also the case in the DGV database (database of genomic variants; dgv.tcag.ca, see Supplementary Figure 6).

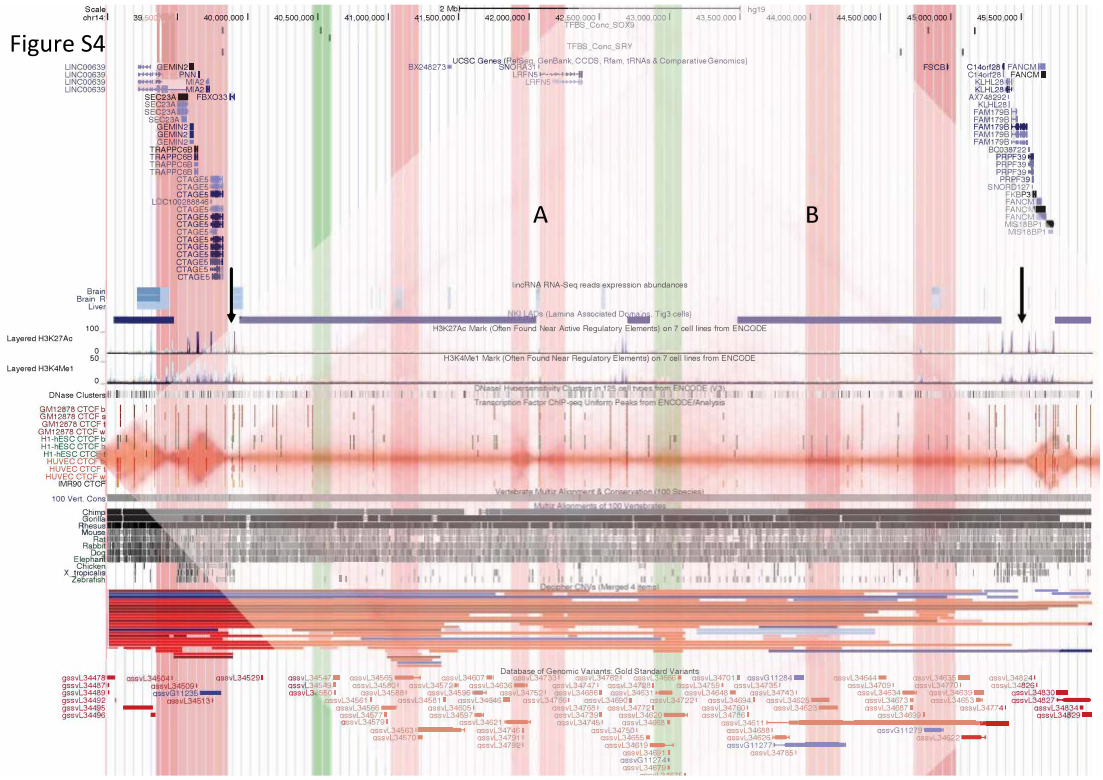

Figure S4

Overview of *LRFN5* locus, taken from the UCSC browser (version GRCh37), with a transparent overlay of the capture-HiC result of the ASD index boy. Lane on top shows computer predicted SOX9 and SRY binding sites, in the middle CTCF binding sites in three different cell types can be found (note that junction B also corresponds to CTCF signals), and on the bottom DECIPHER and DGV copy number variants are found. In both, deletions are more common than duplications. Red vertical bars indicate areas were copy number variants have been found in patients with ID/ASD, and green areas where this so far is not the case.